Refine Search

Search Results -

Terms	Documents
L8 and liposome	9

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Search History

DATE: Thursday, July 05, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L9	L8 and liposome	9	L9
L8	alkylglycerol same (virus or viral or hiv or hsv)	22	L8
L7	L6 and 424/450.ccls.	27	L7
L6	(fatty adj1 acid) same liposome same (viral or virus or Hiv or hsv)	171	L6
L5	lysophospholipid same liposome same (viral or virus or Hiv or hsv)	3	L5
L4	monoglyceride same liposome same (viral or virus or Hiv or hsv)	10	L4
L3	octylglycerol same liposome	1	L3
L2	octylglyderol same liposome	0	L2
L1	alkylglycerol same liposome	5	L1

END OF SEARCH HISTORY

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Terms	Documents
L16 and (424/450).ccls.	31

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Search History

DATE: Thursday, July 05, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L17	L16 and 424/450.ccls.	31	L17
L16	L12 and monoglyceride	460	L16
L15	L14 and 424/450.ccls.	35	L15
L14	L12 and lysophospholipid	202	L14
L13	liposome adj5 (virus or viral or hiv or hsv)	6435	L13
L12	liposome same (virus or viral or hiv or hsv)	26820	L12
L11	octylglycerol and liposome	2	L11
L10	0ctylglycerol and liposome	0	L10
L9	L8 and liposome	9	L9
L8	alkylglycerol same (virus or viral or hiv or hsv)	22	L8
L7	L6 and 424/450.ccls.	27	L7
L6	(fatty adj1 acid) same liposome same (viral or virus or Hiv or hsv)	171	L6
L5	lysophospholipid same liposome same (viral or virus or Hiv or hsv)	3	L5
L4	monoglyceride same liposome same (viral or virus or Hiv or hsv)	10	L4

L3	octylglycerol same liposome	1	L3
L2	octylglyderol same liposome	0	L2
L1	alkylglycerol same liposome	5	L1

END OF SEARCH HISTORY

L1: Entry 4 of 5 File: USPT Sep 19, 2000

DOCUMENT-IDENTIFIER: US 6121245 A
TITLE: Method of treating cancer using alkylglycerols in conjunction with chemotherapy

Detailed Description Text (9):
In another embodiment the administration of the alkylglycerol is intravenous, intramuscular, subcutaneous, topical, or intravenous in the form of a liposome.

Refine Search

Search Results -

Terms	Documents
octylglycerol and liposome	2

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Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L11

Refine Search

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Search History

DATE: Thursday, July 05, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L11	octylglycerol and liposome	2	L11
L10	0ctylglycerol and liposome	0	L10
L9	L8 and liposome	9	L9
L8	alkylglycerol same (virus or viral or hiv or hsv)	22	L8
L7	L6 and 424/450.ccls.	27	L7
L6	(fatty adj1 acid) same liposome same (viral or virus or Hiv or hsv)	171	L6
L5	lysophospholipid same liposome same (viral or virus or Hiv or hsv)	3	L5
L4	monoglyceride same liposome same (viral or virus or Hiv or hsv)	10	L4
L3	octylglycerol same liposome	1	L3
L2	octylglyderol same liposome	0	L2
L1	alkylglycerol same liposome	5	L1

END OF SEARCH HISTORY

L17: Entry 5 of 31 File: PGPB Oct 21, 2004

DOCUMENT-IDENTIFIER: US 20040208921 A1
TITLE: Lipid-drug formulations and methods for targeted delivery of lipid-drug complexes to lymphoid tissues

Current US Classification, US Primary Class/Subclass:
424/450

Summary of Invention Paragraph:
[0004] In order to treat HIV/AIDS-afflicted patients, an aggressive form of therapy was implemented in 1996, known as the "highly active anti-retroviral therapy" or ("HAART"), in which a plethora of drugs are administered to patients systemically. The clinical urgency for drugs having more potent anti-HIV effects has motivated the development of various types of anti-HIV drugs, including nucleoside analogs (e.g., dideoxynucleoside derivatives, including 3'-azido-3'-deoxythymidine ("AZT"), dideoxy cytidine ("ddC"), and dideoxy inosine ("ddI"), protease inhibitors, and phosphonoacids (e.g., phosphonoformic and phosphonoacetic acids). Many of these anti-HIV agents are lipid-derivatized or incorporated into liposomes prior to systemic administration (Hostetler, K Y et al., Methods of treating viral infections using antiviral liponucleotides, Ser. No 09/846,398, US 2001/0033862; U.S. Pat. No. 5,223,263; Hostetler, K Y et al., Lipid derivatives of phosphonoacids for liposomal incorporation and method of use, U.S. Pat. No. 5,194,654; Gagne J. F. et al., Targeted delivery of indinavir to HIV-1 primary reservoirs with immunoliposomes, Biochem Biophys Acta. 1558(2):198-210, [February 2002]). For example, some anti-HIV drugs were encapsulated into the aqueous core of multilamellar and polyethyleneglycerol derivatized liposomes ("PEGylated") (Bergeron, M G. et al., Targeting of infectious agents bearing host cell proteins, WO 00/66173 A3; Bergeron, M G. et al., Liposomes encapsulating antiviral drugs, U.S. Pat. No. 5,773,027; Bergeron, M G. et al., Liposome formulations for treatment of viral diseases, WO 96/10399 A1; Gagne J F et al., Targeted delivery of indinavir to HIV-1 primary reservoirs with immunoliposomes, Biochem Biophys Acta. 1558 (2):198-210, February 2002; Dufresne I et al., Targeting lymph nodes with liposomes bearing anti-HLA-DR Fab' fragments, Biochem Biophys Acta. 1421(2):284-94 [1999]; Bestman-Smith J et al., Sterically stabilized liposomes bearing anti-HLA-DR antibodies for targeting the primary cellular reservoirs of HIV-1 Biochem Biophys. Acta. 1468(1-2):161-74 [2000]; Bestman-Smith J et al., Targeting cell-free HIV and virally-infected cells with anti-HLA-DR immunoliposomes containing amphotericin B, AIDS 10;14(16):2457-65 [2000]; Harvie P, Desormeaux A et al., Lymphoid tissues targeting of liposome-encapsulated 2',3'-dideoxyinosine, AIDS 9(7):701-7 [1995]).

Summary of Invention Paragraph:
[0013] As a drug delivery system, liposomes are especially promising because they can modulate the pharmacokinetics of liposome-associated and encapsulated drugs, which is not possible with non-lipid-associated or "free" drugs (Allen, T. M et al. [1991]; Hwang, K. [1987]; Allen T, et al., Pharmacokinetics of long-circulating liposomes, Adv Drug Del Rev 16:267-284 [1995]; Gabizon A, Liposome circulation time and tumor targeting: Implications for cancer chemotherapy, Adv Drug Del Rev 16:285-294 [1995]; Bethune C, et al., Lipid association increases the potency against primary medulloblastoma cells and systemic exposure of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) in rats, Pharm Res 16:896-903 [1999]). However, therapeutic applications of systemically (IV) administered liposomes have been

limited by the rapid clearance of liposomes from the bloodstream and uptake by RES cells (Alving C, et al., Complement-dependent phagocytosis of liposomes: Suppression by `stealth` lipids, J Liposome Res 2:383-395 [1992]). Incorporation efficiencies for loading many pH-titratable drugs within the interior aqueous compartment of liposomes, including some protease inhibitors such as indinavir, typically have been relatively low (Gagne, J F et al., Targeted delivery of indinavir to HIV-1 primary reservoirs with immunoliposomes, Biochim Biophys Acta 1558(2):198-210 [2002]). Although significant advances have been made in the field of lipid-drug formulation technology in recent years, a need for developing compositions and methods that can provide an effective pharmaceutical-delivery system, which can incorporate drugs and biomolecules or "biologicals" at high efficiency, and deliver stable lipid-pharmaceutical and lipid-biological complexes to a lymphoid tissue is recognized.

Detail Description Paragraph:
[0028] In other embodiments, the drug can be an anticancer drug, an antifungal drug, or an antibacterial drug. In other embodiments, the drug can be an immunomodulatory drug (i.e., an immunoactivator, an immunosuppressant, or an antiinflammatory), such as cyclosporin, steroids and steroid derivatives. Various embodiments of the present invention include the lipid incorporation or lipid-association of a number different types of drugs, and combinations of drugs. For example, liposomes can incorporate a large number of one or more different anti-HIV drugs, anti-fungal drugs, antibacterial drugs, and anti-cancer drugs. In addition to the incorporation of pharmaceutical agents, such as drugs, various types of biologicals may also be included within the interior space of lipid vesicles such as liposomes. The term biologicals include a large number of different biomolecules, such as single or double-stranded forms of DNA and RNA, proteins, glycoproteins, and other biopolymers that can be incorporated by the various method embodiments of the present invention these embodiments are described, throughout this disclosure, using the drug indinavir as an example. Examples of biologicals that can be lipid-incorporated include anti-sense RNAs, single-stranded inhibitory RNA (siRNA), proteins, ribozymes, nucleic acid polymers, proteases, and antibodies. Other embodiments are directed to various drugs and biologicals that may be delivered to lymphoid tissues by lipid vesicles for the treatment of HIV infection and AIDS. Other embodiments are directed to various types of drugs and various types of biologics that may be delivered to lymphoid tissues for the treatment of metastatic breast cancer. For example, drugs (e.g., taxol and DNA intercalating agents) and biologics (e.g., anti-her-2/neu antibodies and anti-sense RNAs) having anti-cancer or anti-proliferative effects may be incorporated within lipid vesicles as lipid-drug and lipid-biological complexes.

Detail Description Paragraph:
[0031] By way of example, indinavir is an HIV protease inhibitor, typically formulated as a sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2- (R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butyl- carboxamido)-piperazinyl))-pentaneamide ethanolate. (e.g., U.S. Pat. No. 5,413,999). Indinavir in pill form (Crixivan.RTM., Merck & Co., Inc., Rahway, N.J.) is typically administered to AIDS patients at a dosage of 800 mg, three times a day. In contrast to the embodiments of the present invention, the U.S. Pat. No. 5,413,999 discloses that indinavir can be taken in a pill form (not lipid-associated), and that the drug should be delivered systemically and not preferentially to lymphoid tissues. Indinavir has about 1000-fold lower solubility in water at neutral pH 7 than at acidic pH 3-4. However, by formulating the lipid-indinavir complex, at a lipid-to-drug molar ratio range from about 5:1 to about 10:1, within a neutral pH range where the aqueous solubility of indinavir is relatively low, 80-100% of an indinavir preparation is incorporated into the liposomes, compared to much lower efficiencies obtained at pH 3-4 (less than 30%), or by other known methods (e.g., Gagne J F et al., Targeted delivery of indinavir to HIV-1 primary reservoirs with immunoliposomes, Biochem Biophys Acta Feb. 1, 2002;1558(2):198-210).

Detail Description Paragraph:
[0034] In addition, other lipids such as steroids, cholesterol, aliphatic amines such as long-chained aliphatic amines and carboxylic acids, long chained sulfates and phosphates, diacetyl phosphate, butylated hydroxytoluene, tocopherols, retinols, and isoprenoid compounds can be intermixed with the phospholipid components to confer certain desired and known properties onto the formed vesicles. In addition, synthetic phospholipids containing either altered aliphatic portions such as hydroxyl groups, branched carbon chains, cycloderivatives, aromatic derivatives, ethers, amides, polyunsaturated derivatives, halogenated derivatives or altered hydrophilic portions containing carbohydrate, glycol, phosphate, phosphonate, quaternary amine, sulfate, sulfonate, carboxy, amine, sulfhydryl, or imidazole groups. Combinations of such groups can be either substituted or intermixed with the above-mentioned phospholipids. It will be appreciated from the above that the chemical composition of the lipid components prepared by the present method can be varied greatly without appreciable diminution of percentage drug capture, although the size of a vesicle can be affected by the lipid composition. Saturated synthetic PC and PG, such as dipalmitoyl can also be used. Other amphipathic lipids that can be used, advantageously with PC, are gangliosides, globosides, fatty acids, stearylamine, long chain alcohols, and the like. PEGylated lipids, monoglycerides, diglycerides, triglycerides can also be included. Acylated and diacylated phospholipids are also useful.

Detail Description Paragraph:
[0041] The embodiments discussed can be further supported in the following examples. In Example 1, the methods employed in the various embodiments of the present invention are provided. In Example 2, the experimental data supporting the pH-dependence of lipid-drug association/incorporation efficiency is provided. Also provided is the data supporting the pH-dependent efficiency of drug release from lipid-associated complexes. Also, in Example 2, the effect of pH on the solubility and lipophilicity of a drug (indinavir) is provided (Table 1A), and the relative sizes and degrees of lipid association for various types of drugs are provided (Table 1B). In Example 3, data supporting enhanced levels of drug delivery to lymphoid tissues are provided by comparing indinavir concentrations in human lymph node (LNMC) and peripheral blood mononuclear cells (PBMCs). In Example 3, a typical time course following HIV-2 infection in monkeys is presented (FIG. 1A). In Example 4, a time course for plasma concentration of indinavir following the subcutaneous administration of lipid-associated and non-lipid-associated indinavir within macaques is provided. In Example 5, the effect of lipid association on the ability of indinavir to inhibit HIV-.sub.287 Replication is provided. In Example 6, a plasma time course profile of free versus lipid-associated indinavir in macaques is provided. In Example 7, the effect of lipid-drug complexes on enhanced accumulation of indinavir in lymph nodes is provided. In Example 8, the effect of lipid-indinavir complex on HIV-2.sub.287 infected macaques is provided. In Example 9, the effect of lipid association on the inhibition of HIV-1 replication in human peripheral blood mononuclear cells is provided. In Example 10, the reduction of HIV viral load in infected macaques by the accumulation of liposome-indinavir complexes in lymphoid tissues is provided.

Detail Description Paragraph:
[0071] It has been reported that changing the pH of indinavir from pH 3 to pH 7 results in a 1000-fold decrease in its aqueous solubility as provided in Table 1A (Lin et al., pH-dependent oral absorption of L-735,524, a potent HIV protease inhibitor, in rats and dogs, Drug Metab Dispos 23:730-735 [1995]). The effect of pH on the ability of indinavir to incorporate or associate with lipid (i.e., liposome) membranes in forming lipid-drug complexes was determined. At a lipid-to-drug ratio of 5:1 (m/m), practically all (85-95%) of the drug in the preparation was found to be associated with liposome at pH 7.4, as illustrated in FIG. 1A. At lower pH values (e.g., pH 4), where aqueous solubility of the drug was higher, a much lower proportion (<30%) of the drug was incorporated into the lipid bilayer of liposomes. Since physiological pH is 7.4, and because biological fluids are highly buffered,

lipid-associated drugs are expected to remain stable under these conditions. The lipid-indinavir complexes formed and maintained at pH 7.4 were used for the subsequent pharmacokinetic studies. Under this set of conditions, lipid-associated indinavir exhibited a diameter of 69.+-.7 nm as provided in Table 1B.

Detail Description Paragraph:
[0079] To determine anti-HIV activity of lipid-associated indinavir, 5.times.10.sup.5 CEM-174 cells were infected with 5.times.10.sup.3 TC.sub.ID50 (multiplicity of infection, MOI=0.01) HIV-2.sub.287 in 2 ml RPMI 1640 tissue culture medium containing 1% fetal calf serum for 1 hr at 37.degree. C. After unabsorbed virus was removed by washing the cells with medium, 100 .mu.l of suspensions containing 10.sup.4 infected cells were transferred to flat-bottom, 96-well microtiter plates containing 100 .mu.l of serially diluted (0-15 .mu.M) indinavir, either in free or liposome-associated formulations. After incubating the cells at 37.degree. C. in RPMI 1640 containing 10% fetal calf serum for 4 days (optimum detection time), the presence of virus-infected cells was determined visually by the presence of syncytia and was subsequently confirmed by ELISA detection of the presence of HIV-2 antigen. Experiments were repeated on at least two different days with each determination done in quadruplicate samples, and the data presented in FIG. 3 are the mean % virus-infected cells. Regression analysis estimated the EC.sub.50 (50% effective inhibitory concentration) value for lipid-associated indinavir to be 0.01-0.025 .mu.M, and 0.05-0.08 .mu.M for free indinavir. These data imply that lipid-associated indinavir is about 3- to 6-fold more potent than free drug in inhibiting HIV-2.sub.287 replication. A similar degree of enhancement was recorded for HIV-1.sub.LAI-infected human PBMC. FIG. 6 shows the concentration-dependent inhibition of HIV-1.sub.LAI replication by the free and lipid-associated indinavir.

Detail Description Paragraph:
[0080] FIG. 4 illustrates a time course for plasma concentration of indinavir following the subcutaneous administration of lipid-associated and non-lipid-associated indinavir within macaques. Young adult male macaques were given either free or liposome-formulated indinavir at 10 mg/kg body mass per dose, and plasma drug concentrations were determined by HPLC assay. Data expressed were means .+-.SD for animals injected with free (open squares, n=4) and liposome-formulated indinavir (other symbols; n=4). Young adult (5-6 kg body mass) macaques that were administered subcutaneously (SC) with either free or lipid-associated indinavir (SC) at 10 mg/kg body mass per single dose. Free indinivir, solubilized in DMSO and phosphate buffer suspension, produced a plasma drug concentration peak at about 0.5-1 hr, and rapidly cleared the drug to below the limit of detection in plasma by 6 hr (FIG. 4). In contrast, lipid-associated indinavir produced a peak plasma concentration about 10-fold lower than free drug, and sustained this plasma level beyond 10 hr. When a second dose was given after a 30-day washout period, a significant amount of drug (>20 ng/ml) remained in plasma beyond 24 hr (FIG. 4; profile of liposome-1 and -2). Animals labeled as liposome-3 (M98165) and -4 (J98328) were previously infected with HIV-2287 and, hence, allowed collection of the visceral lymph nodes for drug analysis. The data are presented in Table 3 provided in Example 7 below.

Detail Description Paragraph:
[0081] In some experiments, lipid-associated indinavir (10 mg/kg body mass) was administered to two additional HIV-2.sub.287-infected macaques, and inguinal lymph nodes were harvested at 6, 24 and 16 or 28 hrs. Drug concentration was measured in blood as well as lymph nodes. Time-course plasma drug concentrations of these two animals are presented in FIG. 4 (liposome-3 and -4).

Detail Description Paragraph:
[0090] To evaluate the role of lipid formulation on indinavir's potency against HIV-1 replication, CD8.sup.+ cells depleted, human peripheral blood mononuclear cells (PBMCs) (previously stimulated with PHA and IL-2, as described in Example 1,

were infected with HIV-1.sub.LAV. The 10.sup.4 HIV-1 infected PBMCs were exposed to 200 .mu.l of serially diluted (0-15 .mu.M) indinavir suspensions in free or liposome-associated formulations expressing either net positive or negative charge. Virus replication was assessed by measuring HIV-1 p24 antigen presence in the culture supernatant. Experiments were repeated on two different occasions with each determination done in duplicate, and the data presented are the mean % inhibition (FIG. 6). Regression analysis estimated the EC.sub.50 value for lipid-associated indinavir to be 0.02-0.03 .mu.M, and >0.15 .mu.M for free indinavir. Even at 15 .mu.M, free indinavir did not exhibit 100% inhibition. These data implies that lipid-associated indinavir is more potent than free drug in inhibition of HIV-1 replication.

Detail Description Paragraph:
Liposome-Indinavir Complexes Accumulate in Lymphoid Tissues and Reduce HIV Viral Load in Infected Macaques

CLAIMS:

15. The lipid-drug complex of claim 1, wherein the lipid includes one or more of phospholipids, sphingolipids, cardiolipins, spingomyelin, glycolipids, gangliosides, cerebrosides, cholesterol, fatty acids, PEG derivatized lipids, monoglycerides, diglycerides, triglycerides.

34. The method of claim 18, wherein the lipid includes one or more of phospholipids, sphingolipids, cardiolipins, spingomyelin, glycolipids, gangliosides, cerebrosides, cholesterol, fatty acids, PEG derivatized lipids, monoglycerides, diglycerides, triglycerides.

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L17: Entry 14 of 31 File: PGPB Oct 25, 2001

DOCUMENT-IDENTIFIER: US 20010033862 A1
TITLE: Methods of treating viral infections using antiviral liponucleotides

Abstract Paragraph:
Compounds are disclosed for treating AIDS, herpes, and other viral infections by means of lipid derivatives of antiviral agents. The compounds consist of nucleoside analogues having antiviral activity which are linked, commonly through a phosphate group at the 5' position of the pentose residue, to one of a selected group of lipids. The lipophilic nature of these compounds provide advantages over the use of the nucleoside analogue alone. It also makes it possible to incorporate them into the lamellar structure of liposomes, either alone or combined with similar molecules. In the form of liposomes, these antiviral agents are preferentially taken up by macrophages and monocytes, cells which have been found to harbor the target HIV virus. Additional site specificity may be incorporated into the liposomes with the addition of ligands, such as monoclonal antibodies or other peptides or proteins which bind to viral proteins. Effective nucleoside analogues are dideoxynucleosides, azidothymine (AZT), and acyclovir; lipid groups may be glycolipids, sphingolipids, phospholipids or fatty acids. The compounds persist, after intracellular hydrolysis, as phosphorylated or non-phosphorylated antiviral nucleosides. The compounds are effective in improving the efficacy of antiviral nucleoside analogues by prolonging the antiviral activity after the administration of the drug has ended, and in preventing retroviral replication in HIV infections which have become resistant to therapy with conventional forms of the antiretroviral agents.

Current US Classification, US Primary Class/Subclass:
424/450

Summary of Invention Paragraph:
[0002] The present invention relates generally to the treatment of viral infections using lipid derivatives of antiviral nucleoside analogues. More particularly, the present invention relates to lipid, and especially phospholipid, derivatives of modified antiviral nucleoside analogues which can be integrated into the structure of liposomes, thereby forming a more stable liposomal complex which can deliver greater amounts of drugs to target cells with less toxicity.

Summary of Invention Paragraph:
[0010] Dideoxynucleoside analogues such as AZT are the most potent agents currently known for treating AIDS, but in a recent human trial, serious toxicity was noted, evidenced by anemia (24%) and granulocytopenia (16%) (2,3). It is desirable, therefore, to provide a means for administering AZT and other dideoxynucleosides in a manner such that the toxic side effects of these drugs are reduced. Further, it is desirable to provide selective targeting of the dideoxynucleoside to monocyte/macrophages to enhance the efficiency of the drug against viral infection in this group of cells. One way to do this is to take advantage of the uptake of liposomes by macrophages.

Summary of Invention Paragraph:
[0014] As previously mentioned, it is now thought that macrophages are an important reservoir of HIV infection (10, 11). Macrophages are also a primary site of

liposome uptake (12, 13). Accordingly, it would be desirable to utilize liposomes to enhance the effectiveness of antiviral nucleoside analogues in treating AIDS and other viral infections.

Summary of Invention Paragraph:
[0018] In order to use nucleoside analogues incorporated into liposomes for treating viral infections more effectively, it is desirable to increase the stability of the association between the liposome and the nucleoside analogue.

Summary of Invention Paragraph:
[0021] The invention provides a composition for use in treating viral infections, including HIV (AIDS), herpes simplex virus (HSV), human herpes virus 6, cytomegalovirus (CMV), hepatitis B virus, Epstein-Barr virus (EBV), and varicella zoster virus (VZV). The composition may contain, in addition to a pharmaceutically acceptable carrier, a lipophilic antiviral agent prepared by chemically linking an antiviral nucleoside analogue to at least one lipid species. The antiviral nucleoside analogue may be linked to the lipid through a monophosphate, diphosphate or triphosphate group. The invention, further, provides a method for incorporating such lipid derivatives of antiviral agents into liposomes for improved delivery of the antiviral agent. A liposome comprises a relatively spherical bilayer which is comprised wholly or in part of the above-described lipid derivatives of antiviral agents. The liposome may also contain pharmacologically inactive lipids. Further, the liposome may contain a ligand, such as a monoclonal antibody to a viral binding site (such as CD.sub.4), or other binding protein. Such a ligand provides additional specificity in the delivery site of the antiviral agent. The invention provides a method for incorporating such ligands into antiviral liposomes.

Summary of Invention Paragraph:
[0028] In another embodiment, the liposome further comprises a ligand bound to a lipid substrate. The ligand may be an antibody, such as a monoclonal antibody to a viral antigen. The viral antigen could be gp41 or gp110 of HIV, or could be any other suitable viral antigen. In one embodiment, the ligand is CD4 receptor protein, or CD4 protein itself. Alternatively, the ligand is an antibody to CD4 or a protein or other substance that binds CD4.

Summary of Invention Paragraph:
[0029] The invention also contemplates a composition for use in treating viral and retroviral infections, comprising a liposome formed at least in part of an lipophilic antiviral agent, the agent comprising a nucleoside analogue having a base and a pentose residue with at least one lipid species attached to the nucleoside analogue through a monophosphate, diphosphate or triphosphate linking group at the 5' hydroxyl of the pentose residue of the nucleoside analogue, and a pharmaceutically acceptable carrier therefore.

Summary of Invention Paragraph:
[0050] Still a further method provided by the present invention is a method of synthesizing a glyceride derivative of a nucleoside analogue, comprising the step of joining a monoglyceride or diglyceride and an antiviral nucleoside monophosphate with a coupling agent in the presence of a basic catalyst. In one embodiment, the glyceride is 1-O-stearoylglycerol and the nucleoside is AZT monophosphate.

Summary of Invention Paragraph:
[0051] Also a part of the present invention is a method for preparing a suspension of liposomes for use in treating viral and retroviral infections in a mammal, comprising providing a lipophilic antiviral agent comprising at least one lipid species attached to a nucleoside analogue through a monophosphate, diphosphate or triphosphate linking group at the 5' position of the pentose residue of the nucleoside, combining the lipophilic antiviral agent and a pharmacologically acceptable aqueous solvent to form a mixture, and forming liposomes from the lipophilic antiviral agent. The liposomes may be formed, for example, by

sonication, extrusion or microfluidization. In one preferred embodiment, the combining step further comprises including in the combination a pharmacologically inactive lipophilic lipid. This inactive lipid can be, for example, a phosphatidylethanolamine, a sphingolipid, a sterol or a glycerophosphatide. The method also may include treating the liposomes with thio-antibodies to produce immunoliposomes, or including in the combination an lipophilic lipid which is, in part, comprised of a ligand. Thus, the liposome may include a ligand bound to a lipid substrate.

Detail Description Paragraph:
[0085] Lipids suitable for coupling to nucleosides, comprising primarily long chain fatty acids or alcohols, monoglycerides or diglycerides, ceramides and other lipid species described below, may be phosphorylated by treatment with appropriate agents, for example using phenyl phosphorodichloridate according to the procedure of Brown (32), by treatment with phosphorus oxychloride as in Example 6, or by other known phosphorylation procedures.

Detail Description Paragraph:
[0142] The liposomes with the above formulations may be made still more specific for their intended targets with the incorporation of monoclonal antibodies or other ligands specific for a target. For example, monoclonal antibodies to the CD4 (T4) receptor may be incorporated into the liposome by linkage to phosphatidylethanolamine (PE) incorporated into the liposome by the method of Leserman, et al. (19). As previously described, HIV will infect those cells bearing the CD4 (T4) receptor. Use of this CD4-targeted immunoliposome will, therefore, focus antiviral compound at sites which HIV might infect. Substituting another CD4 recognition protein will accomplish the same result. On the other hand, substituting monoclonal antibody to gp110 or gp41 (HIV viral coat proteins) will focus antiviral immunoliposomes at sites of currently active HIV infection and replication. Monoclonal antibodies to other viruses, such as Herpes simplex or cytomegalovirus will focus active compound at sites of infection of these viruses.

Detail Description Paragraph:
[0193] Liposomes containing 10 mole percent of either dimyristoylphosphatidylazidothymidine (LN1), dimyristoylphosphatidyldideoxythymidine (LN2) or azidothymidine diphosphate dimylristoylglycerol (LN4) in the indicated concentrations were tested for their ability to inhibit HIV replication in CEM (wild type) cells in vitro. All three of these antiretroviral liponucleotides inhibited HIV p24 production; the amounts of drug required to reduce virus production by 50% (E.D. 50) were as follows:

Detail Description Paragraph:
[0198] Dideoxythymidine (N2) is a weak inhibitor of HIV p24 production. Surprisingly, phosphatidyldideoxythymidine (LN2) is somewhat more effective than the free nucleoside. As can be seen in the chart, slightly more free ddT is required to reduce p24 production than with phosphatidyldideoxythymidine. Control liposomes (CONT) at a matched total phospholipid concentration are without effect.

Detail Description Paragraph:
[0204] In this experiment, antiviral protection provided by preincubation with dimyristoylphosphatidylazidothymidine (LN1) in liposomes prepared as noted above was compared with that of free azidothymidine (N1). CEM (wild type) cells were preincubated for 3 days under standard conditions in RPMI media containing 7.14 pM of either free AZT (N1) or phosphatidylAZT (LN1). The cells were then washed twice with PBS, and fresh RPMI media added. Each group of cells was then divided into three batches. One batch was immediately infected with HIV, as noted above; after washing away unattached HIV, the sample was allowed to incubate in media alone for 3 days. Two other batches were allowed to incubate in media alone for either 24 or 48 hours to allow any intracellular antiviral agent present to become depleted. Then they were infected with HIV, the cells washed free of virus, and fresh RPMI

media added. After 3 days of further incubation, the supernates of all batches were tested for the presence of p24 protein.

Detail Description Paragraph:
[0232] It should be apparent from the foregoing that other nucleoside analogues and phospholipid derivatives thereof can be substituted in the Examples to obtain similar results. AZT-monophosphate or other antiviral nucleoside phosphate may also be contained in the aqueous compartments of the liposome. The molar percentage of the lipid antiviral nucleoside may vary from 0.1 to 100% of the total lipid mixture. Furthermore, mixtures of antiviral nucleoside lipids may be used in constructing the liposomes for therapy of viral diseases. It should be further emphasized that the present invention is not limited to the use of any particular antiviral nucleoside analogue; rather, the beneficial results of the present invention flow from the formation of liposomes from the lipid derivatives of these materials. Thus, regardless of whether an antiviral nucleoside is presently known, or whether it becomes known in the future, the methods of forming the presently-contemplated lipid derivatives therefrom are based on established chemical techniques, as will be apparent to those of skill in the art, and their incorporation into liposomes is broadly enabled by the preceding disclosure. It should be emphasized again that the present syntheses are broadly applicable to formation of compounds from essentially all nucleoside analogues for use in the practice of the present invention.

CLAIMS:

47. A method of synthesizing a glyceride derivative of a nucleoside analogue, comprising the step of joining a monoglyceride or diglyceride and an antiviral nucleoside monophosphate with a coupling agent in the presence of a basic catalyst.

57. A method for preparing a suspension of liposomes for use in treating viral infections in a mammal, comprising: providing a lipophilic antiviral agent comprising at least one lipid species attached to a nucleoside analogue; combining the lipophilic antiviral agent and a pharmacologically acceptable aqueous solvent to form a mixture; and forming liposomes from the lipophilic antiviral agent.

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L17: Entry 27 of 31 File: USPT Oct 6, 1998

DOCUMENT-IDENTIFIER: US 5817638 A
TITLE: Antiviral liponucleosides: treatment of hepatitis B

Abstract Text (1):
Compounds for treating hepatitis B infections. The compounds consist of nucleoside analogues having anti-hepatitis B activity which are linked, commonly through a 5' phosphate of the pentose residue, to one of a selected group of lipids. The lipophilic nature of these compounds provides an advantage over the use of the nucleoside analogue alone, making it possible to incorporate them into the lamellar structure of liposomes, either alone or in combination with similar lipid molecules. In the form of appropriately sized liposomes, these anti-hepatitis B agents are preferentially taken up by the liver cells which have been found to harbor the target virus.

Brief Summary Text (2):
The present invention relates to the treatment of infections of hepatitis virus using lipid derivatives of antiviral nucleoside analogues. More particularly, the present invention relates to lipid, especially phospholipid, derivatives of antiviral nucleoside analogues which can be integrated into the structure of liposomes, thereby forming a more stable liposomal complex that can deliver greater amounts of antihepatitis drugs to target cells with less toxicity.

Detailed Description Text (2):
The present invention involves lipid derivatives of nucleoside analogues having an inhibiting effect on the replication of hepatitis B virus. As lipid derivatives or liponucleotides, these antiviral agents can be stably incorporated into the lipid bilayer of liposomes. These lipid derivatives can be converted into nucleoside analogue triphosphates by constituent cellular metabolic processes, and have antiviral effects in vivo and in vitro.

Detailed Description Text (5):
Any antiviral nucleoside having the ability to inhibit the replication of hepatitis virus B virus is suitable for use in the compositions and methods of the invention. In general, the nucleoside analogues used in preparing the lipid derivatives and liposomes of the present invention will have a purine or pyrimidine base, e.g., adenine, guanine, cytosine or thymine, or an analogue thereof, attached to a pentose, such as ribose, arabinose, or a ribose or arabinose residue and/or derivative. The attachment is through the nitrogen in the 9-position of the purines or through the nitrogen in the 1-position of the pyrimidines. These nitrogens are linked by a .beta.-N-glycosyl linkage to carbon 1 of the pentose residue.

Detailed Description Text (18):
Suitable phospholipids comprise phosphoglycerides, sphingolipids, or acyl phosphates. Phosphorylated nucleoside analogues are known. The dideoxynucleoside analogue is phosphorylated according to conventional procedures such as the phosphorous oxychloride method of Yoshikawa et al. (7,8) or Toorchen and Topal (9). The preferred modified analogue is the 5'-monophosphate. Lipids suitable for coupling to nucleosides, comprising primarily long chain fatty acids or alcohols, monoglycerides or diglycerides, sphingosines and other lipid species described below, may be phosphorylated by treatment with appropriate agents, for example

using phenyl phosphorodichloridate according to the procedure of Brown (10), by treatment with phosphorus oxychloride, or by other known phosphorylation procedures.

Detailed Description Text (55):
In an HBV-infected patient, the virus proliferates within infected cells, and in order to treat the disease and prevent the replication of viral DNA, the antiviral agent must be administered to the patient in a manner capable of introducing the agent initially into the bloodstream and ultimately into the cells. In consideration of this data and the finding that appropriate sizing of liposomes achieves highly efficient uptake into a site of hepatitis B infection in the liver, it is anticipated that the lipid derivatives of any antihepatitis B nucleoside, incorporated into liposomes of effective small diameter, will be effective in vivo at lower doses with anticipated lower toxicity.

Detailed Description Text (125):
A patient suffering from active hepatitis B infection is treated by parenteral administration of liposomally incorporated DMP-FIAU at a dose of 1 mg/kilo/day of the active FIAU moiety until a clinical response indicating the inhibition of production of hepatitis B virus is observed. Liposomes incorporating DMP-FIAU are prepared using a microemulsification apparatus (MICROFLUIDIZER.RTM.microemulsifier, Newton, Mass.), as indicated in Example 6. The dose of FIAU can be adjusted from 1/100th of the indicated dose to 10 times the indicated dose, as determined by clinical judgment. An effective response to hepatitis therapy with DMP-FIAU lipid prodrug is measured by absence of detectable virus particles in the serum of the patient and clinical improvement in the patient.

Current US Cross Reference Classification (1):
424/450

Other Reference Publication (37):
Kende, et al. (1985), "Enhanced efficacy of liposome-encapsulated rebavirin against rift valley fever virus infection in mice," Antimicrob. Agents Chemother., 27:903-907.

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L2: Entry 3 of 3 File: PGPB Nov 21, 2002

DOCUMENT-IDENTIFIER: US 20020173489 A1
TITLE: COMPOSITIONS CONTAINING A MIXTURE OF PHOSPHOROUS COMPOUNDS AND ALKYLGLYCEROLS

Detail Description Paragraph:
[0057] Alkylglycerol-water mixtures which contain, for example, nonylglycerol, octylglycerol, hexylglycerol, pentylglycerol, propylglycerol or ethylglycerol are preferred. Preferably, such aqueous mixtures contain 3 of the said glycerol ethers, namely, a lower (ethyl, propyl), a middle (pentyl, hexyl) and a higher (nonyl, octyl) alkyl glycerol, where the amount by weight of the lower ether is about as great as the sum of the amounts by weight of the two other glycerol ethers. The amount of water is about the same as the amount of lower glycerol ether and amounts, for example, to half of the total amount of the glycerol ethers present. Examples for such glycerol ether-water mixtures are set out in the following:

Detail Description Paragraph:
[0089] The compounds and compositions are particularly useful in the treatment of conditions involving viruses with a lipid membrane. Exemplary of such viruses are wart (Verruca) viruses, such as Verruca accuminata, Verruca plantaris, Verruca senilis, and Verruca vulgaris, as well as Epidermodysplasia Verruciformis, influenza virus, hepatitis C virus, adenovirus, and Herpes simplex virus. In the treatment of conditions involving viruses such as those described supra, the mode of administration will vary; however, it is preferred to administer the compounds and compositions topically, although other forms of administration, such as those set forth supra, are also appropriate.

Detail Description Paragraph:
[0136] The following example demonstrates the efficacy of compounds in accordance with the invention in the treatment of virus mediated disorders.

CLAIMS:

26. The composition of claim 23, which contains as component b) a mixture of three alkylglycerols, one of which is nonyl- or octylglycerol, another is hexyl- or pentylglycerol, and the third is propyl- or ethylglycerol, and water.

47. A method for treating a patient with a viral infection comprising administering an antiviral effective amount of the compound of claim 1 to said patient.

49. The method of claim 47, wherein said viral infection is caused by a virus with a lipid membrane.

50. The method of claim 47, wherein said viral infection is caused by Verruca accuminata, Verruca plantaris, Verruca senilis, Verruca vulgaris, or Epidermodyplasia verruciformis.

51. The method of claim 47, wherein said viral infection is caused by influenza virus, hepatitis C virus, adenovirus, human immunodeficiency virus or herpes

simplex virus.

52. A method for treating a patient with a viral infection, comprising administering an antiviral effective amount of the composition of claim 15 to said patient.

55. The method of claim 52, wherein said viral infection is caused by a virus with a lipid membrane.

56. The method of claim 52, wherein said viral infection is caused by Verruca accuminata, Verruca plantaris, Verruca senilis, Verruca vulgaris, or Epidermodyplasia verruciformis.

57. The method of claim 52, wherein said viral infection is caused by influenza virus, hepatitis C virus, adenovirus, human immunodeficiency virus, or herpes simplex virus.

58. A method for treating a patient with a viral infection, comprising administering an antiviral effective amount of the composition of claim 21 to said patient.

60. The method of claim 58, wherein said viral infection is caused by a virus with a lipid membrane.

61. The method of claim 58, wherein said viral infection is caused by Verruca accuminata, Verruca plantaris, Verruca senilis, Verruca vulgaris or Epidermodyplasia Verrucifornis.

62. The method of claim 58, wherein said viral infection is caused by influenza virus, hepatitis C virus, adenovirus, human immunodeficiency virus, or herpes simplex virus.

63. A method for treating a patient with a viral infection, comprising administering an antiviral effective amount of the composition of claim 23 to said patient.

65. The method of claim 63, wherein said viral infection is caused by a lipid membrane containing virus.

66. The method of claim 63, wherein said viral infection is caused by Verruca accuminata, Verruca plantaris, Verruca senilis, Verruca vulgaris, or Epidernodyplasia verruciformis.

67. The method of claim 63, wherein said viral infection is caused by influenza virus, hepatitis C virus, adenovirus, human immunodeficency virus, or herpes simplex virus.

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L3: Entry 2 of 2 File: USPT Jul 25, 1995

DOCUMENT-IDENTIFIER: US 5436234 A
TITLE: Eurcyl, brassidyl and nervonyl derivatives

Brief Summary Text (26):
The compounds according to the present invention can also be used in combination with alkylglycerols of the general formula: ##STR17## wherein one of the substituents R.sup.3 and R.sup.4 is an alkyl radical containing 2 to 12 carbon atoms and the other one is a hydrogen atom. Such a pharmaceutical composition preferably contains an alkylglycerol mixture of nonyl- or octylglycerol, hexyl- or pentylglycerol and propyl- or ethylglycerol, as well as water. Such pharmaceutical composition combinations of alkylglycerols and phospholipids and the preferred contents of the individual active materials are described in DE-OS 36 41 379. The pharmaceutical compositions which contain a compound according to the present invention in combination with at least one alkylglycerol are especially suitable for topical application.

Detailed Description Text (86):
The preparation of a hexadecylphosphocholine formulation in liposomes takes place according to DE 40 26 136.0. 12 mmol hexadecylphosphocholine, 15 mmol cholesterol and 3 mmol DPPG are dissolved in 200 ml propan-2-ol with warming. The solvent is then stripped off in a vacuum and the fine-divided lipid film is mixed with 300 ml phosphate buffer solution (pH 7.0). Subsequently, the mixture is maintained at 40.degree. C. for 60 minutes while slowly rotating.

Detailed Description Text (87):
Subsequently, the lipid suspension obtained is transferred into the pressure cell of a French press and pressed out at 740 MPa and this procedure is repeated three times. The liposome dispersion formed is then centrifuged for 30 minutes at 27000 g and 5.degree. C. and the supernatant recovered.

Detailed Description Paragraph Table (1):
TABLE _____ amount/ active material formulation day action.sup.+ _____ hexadecylphospho- liposomes 30 .mu.mol <10% choline 10 .mu.mol -90% erucylphospho- in physiol. 10 .mu.mol <10% choline NaCl sol. 6 .mu.mol <10% 3 .mu.mol <10%
_____ .sup.+ residual weight of the tumour in %, referred to the untreated control.

CLAIMS:

12. The pharmaceutical composition according to claim 11, wherein a mixture of nonyl- or octylglycerol, hexyl- or pentylglycerol and propyl- or ethylglycerol and water are present in the composition.

L5: Entry 10 of 16 File: USPT Oct 9, 2001

DOCUMENT-IDENTIFIER: US 6299897 B1
TITLE: Inhibition of selectin binding

Drawing Description Text (2):
FIG. 1 is a drawing of two polymerized glycoliposomes showing an expanded detail of the chemical structure. Structure "A" is able to inhibit the binding of P-selectin to HL-60 cells at an oligosaccharide concentration below 2 nM, while Structure "B" has essentially no activity. The vesicles are unilamellar and made up of single-chain lipids with diyne groups cross-linked using UV light. Conjugated to about 5% of the lipids are analogs of the sLe.sup.x oligosaccharide. The preparations differ in terms of the outward facing determinants displayed by the neighboring lipids. In structure "A", the neighboring lipids provide carboxylic acid groups, which have a negative charge at neutral pH. In structure "B", the neighboring lipids are neutral. The negatively charged lipids work synergistically with the sLe.sup.x analog to supply P-selectin binding activity, just as sulfotyrosine works synergistically with sLe.sup.x in the natural ligand. P- and L-selectin differ from E-selectin in the requirement for a negative charge determinant in binding.

Other Reference Publication (10):
Spevak Et Al., Polymerized Liposomes Containing C-Glycosides of Sialic Acid: Potent Inhibitors of Influenza Virus in Vitro Infectivity, J. Am. Chem. Soc., 1993, pp. 1146-1147, No. 115.

Refine Search

Search Results -

Terms	Documents
L4 and (virus or viral or hiv or hsv)	16

Database: US Pre-Grant Publication Full-Text Database; US Patents Full-Text Database; US OCR Full-Text Database; EPO Abstracts Database; JPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L5

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Thursday, July 05, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L5	L4 and (virus or viral or hiv or hsv)	16	L5
L4	(single adj1 chain adj1 lipid)	56	L4
L3	L1 and liposome	2	L3
L2	L1 and (virus or viral or hiv or hsv)	3	L2
L1	octylglycerol	16	L1

END OF SEARCH HISTORY

L5: Entry 11 of 16 File: USPT Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5985852 A
TITLE: Inhibition of selectin binding

Drawing Description Text (2):
FIG. 1 is a drawing of two polymerized glycoliposomes showing an expanded detail of the chemical structure. Structure "A" is able to inhibit the binding of P-selectin to HL-60 cells at an oligosaccharide concentration below 2 nM, while Structure "B" has essentially no activity. The vesicles are unilamellar and made up of single-chain lipids with diyne groups cross-linked using UV light. Conjugated to about 5% of the lipids are analogs of the sLe.sup.x oligosaccharide. The preparations differ in terms of the outward facing determinants displayed by the neighboring lipids. In structure "A", the neighboring lipids provide carboxylic acid groups, which have a negative charge at neutral pH. In structure "B", the neighboring lipids are neutral. The negatively charged lipids work synergistically with the sLe.sup.x analog to supply P-selectin binding activity, just as sulfotyrosine works synergistically with sLe.sup.x in the natural ligand. P- and L-selectin differ from E-selectin in the requirement for a negative charge determinant in binding.

Other Reference Publication (47):
Reichert et al., "Polydiacetylene liposomes functionalized with sialic acid bind and colorimetrically detect influenza virus" J. Am. Chem. Soc. (1995) 117:829-830.

Other Reference Publication (54):
Spevak et al., "Polymerized liposomes containing C-glycosides of sialic acid: Potent inhibitors of influenza virus in vitro infectivity" J. Amer. Chem. Soc. (1993) 115:1146-1147.

L5: Entry 13 of 16 File: USPT Oct 17, 1995

DOCUMENT-IDENTIFIER: US 5459127 A

**** See image for Certificate of Correction ****

TITLE: Cationic lipids for intracellular delivery of biologically active molecules

Brief Summary Text (8):

Various techniques for introducing the DNA or mRNA precursors of bioactive peptides into cells include the use of viral vectors, including recombinant vectors and retroviruses, which have the inherent ability to penetrate cell membranes. However, the use of such viral agents to integrate exogenous DNA into the chromosomal material of the cell carries a risk of damage to the genome and the possibility of inducing malignant transformation. Another aspect of this approach which restricts its use in vivo is that the integration of DNA into the genome accomplished by these methods implies a loss of control over the expression of the peptide it codes for, so that transitory therapy is difficult to achieve and potential unwanted side effects of the treatment could be difficult or impossible to reverse or halt.

Brief Summary Text (12):

A significant body of information is emerging regarding the use of other cationic lipids for the delivery of macromolecules into cells. Loyter prepared vesicles containing a quaternary ammonium surfactant that are capable of transferring functional tobacco mosaic virus into plant protoplasts. (Ballas, N., Zakai, N., Sela, I. and Loyter, A. Biochim. Biophys Acta 939 8-18 (1988)). Huang used cetyltrimethylammonium bromide to obtain functional expression from the chloramphenicol acetyl transferase gene transfected into mouse fibroblasts (Pinnaduwage, P., Schmitt, L. and Huang, L. Biochim. Biophys Acta 985 33-37 (1989)). Behr has shown that a novel lipophilic derivative of spermine can transfect primary pituitary cells (Behr, J.-P., Demeneix, B., Loeffler, J.-P. and Perez-Mutul, J. Proc. Natl. Acad. Sci. USA 86 6982-6986 (1989)). Finally, John Silvius has shown that a cationic lipid (DOTAP), originally synthesized by Eibl (Eibl, H. and Woolley, P. Biophys. Chem. 10 261-271 (1979)) forms liposomes which can fuse with negatively charged liposomes and can deliver functional DNA and RNA into tissue culture fibroblasts (Stamatatos, L., Leventis, R., Zuckermann, M. J. & Silvius, J. R. Biochemistry 27 3917-3925 (1988)). Other laboratories have studied the physical properties of vesicles formed from synthetic cationic amphophiles (Rupert, L. A. M., Hoekstra, D. and Engberts, J. B. F. N. Am. Chem. Soc. 108: 2628-2631 (1985); Carmona-Ribeiro, A. M., Yoshida, L. S. and Chaimovich, H. J. Phys Chem 89 2928-2933 (1985); Rupert, L. A. M., Engberts, J. B. F. N. and Hoekstra, D. J. Amer. Chem. Soc. 108:3920-3925 (1986)).

Detailed Description Text (22):

In other pharmaceutical products of the invention the therapeutic agent is a polynucleotide. In one of these embodiments, the therapeutic polynucleotide is a ribozyme, or an antisense RNA or DNA. In preferred embodiments, the formulation comprises an antisense DNA or RNA or a ribozyme directed against HIV. In a particularly preferred embodiment, the therapeutic polynucleotide is an antisense DNA or RNA or a ribozyme directed against the rev transactivator of HIV. An example of such an agent is the 28-mer phosphorothioate antisense polynucleotide. Alternatively, the therapeutic polynucleotide can be one coding for an immunogen, a natural hormone, or a synthetic analogue of a natural hormone; or it can be a polynucleotide sequence coding for a gene product that is deficient or absent in a

disease state, and administration of said product to a human in need of therapy relating to said gene product has a therapeutic effect.

Detailed Description Text (86):
According to current theories of self-assembling lipid structures, the combined thermodynamic forces of packing constraints and the interactive free energies of lipid polar headgroups with an aqueous media determine the geometry and structure of lipid vesicles. Entropy favors small structures, and packing constraints oppose close packing. Accordingly, in an aqueous media, the entropically favored structures for homogenous systems of single-chain lipids are single layer micelle structures having a relatively small radius of about 15-20 Angstrom units, while those for corresponding systems of double-chain lipids, whose lipid chains cannot be so tightly packed, are double layered structures having aqueous interiors with wall thicknesses of about 50 Angstroms (Israelachvili, J. N. et al., Biochim. Biophys. Acta 470:185-201 (1977).

Detailed Description Text (88):
It is believed that the presence of effective concentrations of single chain lipids in the lipid formulation opposes fusogenic behavior leading to aggregation, while preserving the fusogenic behavior that allows vesicle contents to be delivered into cells. Single chain lipids can shift the thermodynamic equilibria of lipid systems to allow closer packing and to favor the stability of formed lipid vesicles so as to resist aggregation. As levels of single-chain lipids increase, however, the efficiency of transfection no longer is improved, but declines. This effect may be due to an increase in the resistance of the lipid vesicles to fusion which inhibits fusion with cell membranes or to toxic properties of the single-chain (lyso) lipids, or to both effects.

Detailed Description Text (110):
Particularly preferred contemplated uses of the invention are deliveries of either an antisense polynucleotide or ribozyme as described above, and having as its target the rev site of the HIV genome (Scientific American, October, 1988, pp. 56-57). Matsukura, M. et al. Proc. Nat'l. Acad. Sci. 86:4244-4248 (1989) describe a 28-mer phosphorothioate compound anti-HIV (anti-rev transactivator) specific for the site.

Detailed Description Text (111):
Other therapeutic uses of cationic lipids herein disclosed include the liposomal delivery of nucleoside or nucleotide analogues having an antiviral effect, such as dideoxynucleotides, didehydronucleotides, nucleoside or nucleotide analogues having halo-substituted purine or pyrimidine rings such as 5-trifluoromethyl-2'-deoxyuridine or 5-flurouracil; nucleoside or nucleotide analogues having halo- and azido-substituted ribose moieties, such as 3'-azido-3'deoxythymidine (AZT), nucleoside analogues having carbon substituted for oxygen in the ribose moiety (carbocyclic nucleosides), or nucleotide analogues having an acyclic pentose such as acyclovir or gancyclovir (DHPG). The liposomal delivery of such analogues is disclosed in U.S. patent application Ser. No. 099,755 filed September, 1987 by Hostetler and Richman. The antiviral potency of these analogues is found to be increased when they are presented to the cells as phospholipid derivatives. These derivatives may be incorporated into the liposomal structure for administration to cells thereby forming a more stable liposomal complex which can deliver greater amounts of drugs to target cells with less toxicity. Effective antiviral lipid derivatives of nucleoside analogues comprise phosphatidyl 2',3'-dideoxynucleosides, 2'3'-didehydronucleosides, 3'-azido-2'-deoxynucleosides, 3'-fluorodeoxynucleosides and 3'-fluorodideoxynucleosides, 9-.beta.-D-arabinofuranosyladenine (araA), 1-.beta.-D-arabinofuranosylcytidine (araC), nucleosides such as acyclovir and gancyclovir having an acyclic ribose group, or the same nucleoside analogues as diphosphate diglyceride derivatives. Preferred species of lipid derivatives of antiviral or antiretroviral nucleoside analogues for the treatment of HIV infection using cationic lipid mediated liposomal delivery are phospholipid derivatives of

3'-azido-2',3'-dideoxypyrimidine, 3'-halopyrimidine dideoxynucleoside, or a 2',3'-didehydro-2',3'-dideoxynucleoside, for example, phosphatidyl 3'-azido-3'deoxythymidine (pAZT) or phosphatidyl 2-chlorodeoxyadenosine. Certain viral infections, comprising herpes, cytomegalovirus, and hepatitis B infections are effectively treated with nucleoside analogues comprising acyclovir, gancyclovir, 1-(2-deoxy-2'-fluoro-1-.beta.-D-arabinofuranosyl)-5-iodocytosine (FIAC) or 1(2'-deoxy-2'-fluoro-1-.beta.-D-arabinofuranosyl)5-iodouracil (FIAU). Phospholipid derivatives of these agents, preferably the phosphatidyl and diphosphate diglyceride derivatives can be administered in these diseases using cationic lipid liposomal delivery systems, according to the invention. Details of the structures, synthesis and liposomal delivery of lipid derivatives of antiviral nucleosides are presented in U.S. patent applications Ser. Nos. 216,412; 319,485; and 373,088 which are hereby incorporated by reference.

Other Reference Publication (28):
Matsukura. M., et al. (1989) Regulation of viral expression of human immunodeficiency virus in vitro by an antisense phosphorothioate oligodeoxynucleotide against rev (art/trs) in chronically infected cells. Proc. Natl. Acad. Sci. USA 86:4244-4248.

Other Reference Publication (31):
Meyer, K. L., et al. 91991) In vitro evaluation of phosphocholine and quaternary ammonium containing lipds as novel anti-HIV agents. J. Med. Chem. 34:1377-1383.

CLAIMS:

27. A pharmaceutical preparation according to claim 26, wherein said ribozyme or antisense DNA or RNA is directed against HIV.

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L5: Entry 15 of 16 File: USPT May 7, 1991

DOCUMENT-IDENTIFIER: US 5013556 A
TITLE: Liposomes with enhanced circulation time

Brief Summary Text (57):
Also included in the invention is a method for delivering a drug selectively to a target tissue or cell type characterized by surface-bound tissue-specific ligand-binding molecules. A suspension of liposomes containing a surface-bound ligand effective to bind specifically and with high affinity to said ligand-binding molecule, and between 1-20 mole percent of an amphipathic lipid derivatized with a polyalkylether is administered parenterally. The target tissue may be a disease-related tissue, such as a solid tumor, or a circulating cell type, such as a virus-infected blood cell having virus-specific surface antigens.

Detailed Description Text (10):
Another amphipathic lipid which may be employed is cholesterol and related sterols. In general, cholesterol may be less tightly anchored to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore be less effective in promoting liposome evasion of the RES in the bloodstream. Similarly, single-chain lipids, such as long-chain fatty acids, may be derivatized with a polyalkylether, but provide less effective anchoring to the bilayer membrane than a lipid having two or more hydrocarbon chains.

Detailed Description Text (46):
As another example, the liposomes may be prepared with surface-bound ligand molecules, such as antibodis, which are effective to bind specifically and with high affinity to ligand-binding molecules, such as antigens, which are localized specifically on target cells. As an example, the ligand molecules may be tumor-specific antibodies, for binding to tumor-specific antigens on tumor cells. As another example, the ligand may be a CD4 peptide, effective to bind specifically to HIV-infected T cells.

Detailed Description Text (50):
In still another application, the liposome composition is designed to enhance uptake of circulating cells or other blood-borne particles, such as bacteria, virus-infected blood cells and the like. Here the long-life liposomes are prepared to include surface-bound ligand molecules, as above, which bind specifically and with high affinity to the selected blood-borne cells. Once bound to the blood-borne particles, the liposomes can enhance uptake by the RES.

CLAIMS:

17. The composition of claim 15, wherein the surface-bound ligand is CD4 peptide which is effective to bind to HIV-infected T cell or B cells.

33. The method of claim 19, wherein the cells are HIV-infected T-cells or B cells and the surface-bound D4 peptide.